Marine Biological Laboratory
WOODS HOLE, MASSACHUSETTS

Aug 1949

Dear Josh:

I am sending under separate cover a provisional copy of the paper which Amos Norman and I would like to send to PNAS via Delbruck.

Note that the n<u>hit</u> theory (equation 2) is the same as the one you arrived at and as far as I can see it cannot be made less cumbersome except where terms of the order of $\frac{KD^n}{n!}$ can be ignored. This theory in its cumbersome form is the one on which practically all of the multi-hit work in the literature has been interpreted. As you will see, I don't think it is the correct theory to use in interpreting survival curves anyway.

The equation $q = e^{-ne^{-kD}}$ attributed to Delbruck is given without derivation and I am not certain what his starting premises were, i.e. whether the Poisson is that due to phage absorbtion in which case the proportion of infective centers when no dose is delivered is $1-e^{-n}$, or whether it is due to the randomizing effect of radiation, where the expression holds only at high dose. In other words, it is not clear whether the expression is intended to apply to experiments with freshly absorbed phage, or following intracellular growth. In the former case it is erroneous because multiplicity reactivation can take place. (Compare our equations 17 and 23). In any case, if Delbruck's equation means the same thing as our equation 16, then you are correct in saying that the plot of $\log\log(1/q)$ versus D will not remain linear all the way to the D = 0 intercept; in fact it becomes infinite at D = 0.

Note that the way we have handled this is to use the deviation from linearity of this plot in the low dose range to indicate the type of distribution of the sensitive units pertaining at D = 0. Also note that the second derivative of this plot can never change sign if $q = (1-e^{-k})^n$. Therefore, an inflection point in the plot is an indication that the data are best described by equation 21 or 20. (Unless you think the n-<u>hit</u> theory is still defensible).

I am indebted to you for urging me to read Luria and Dulbecco's March genetics paper because it made evident the need for generalizing the multi-process case as we have done in equation 21. Their equations are correct and their derivation is very neat if you already know what they are driving at, but there is considerable confusion in the text due to the inconsistent usage of the terms 'effective hit' and 'lethal mutation', neither of which are actually intended by the symbol r. If r is taken to mean the dose corresponding to a hypothetical number of effective hits, re^{-r} of which are actually

effective, everything comes out right. A very minor flaw is the failure to exclude the singly infected bacteria which yield plaques from the numerator of the experimental value w, when it is so excluded in the calculation of the theoretical value y. This leads to a maximum error of about 4% at low dose and low multiplicity, in the experiments reported. The thing that bothers me most is that they don't recognize the importance of the effect that unequal sensitivity of the units will have on the apparent value of y. On p. 113, next to last paragraph, this is glossed over. Actually, unequal sensitivity will cause the apparent value of $\hat{m}$ to become a function of both dose and multiplicity, since the less sensitive units will contribute negligibly toward decreasing the probability of reactivation at low dose and high multiplicity, but will greatly lower this probability at high dose and low multiplicity. However, the relative effect* of increasing dose will be greater at high multiplicities. I think that this may account for much of the discrepancy between w and y in figs. 2 & 4. I don't think I've made this clear, but maybe you can figure it out.

The interpretation of the Neurospora data given in the ms. has some testable consequences, one of which is that the frequency of allelism among non-dissociating components should be very high.

I hope you have some comments to make on the ms. (which there is no need to return as I have other copies.) Also, I would like your prognosis on our chances of having it published via Delbruck. I'm not worried about that Yule ref. but will try to find it in the lib. here. By the way, now what do tou make of Witkin's case in the light of our analyses?

sincerely,

Kim

P.S. I like your idea for successive approximation, but shouldn't your equation (5) read: $\log\log(1-e^{-n})/q_r = \log n - ad$? Let me know how you make out irradiating diploid K-12.

*relative to y computed on the basis of equal sensitivity.